IN THE SPECIFICATION

INSERTION(S):

Please add the following section headings and paragraphs to the specification as originally filed.

At page 1, please insert the following new section headings and paragraphs.

CROSS REFERENCE TO RELATED APPLICATIONS

[0000] This application is a U.S. national stage filing under 35 U.S.C. §371 of International Application No. PCT/EP2005/003013 filed on March 22, 2005, which claims priority of German Application No. DE 10 2004 014 841 filed on March 24, 2004. This application contains subject matter that may relate to presently filed and co-assigned U.S. Applications titled "Use of rotigotine for treatment or prevention of dopaminergic neuron loss" (Serial No. 11/060,997) and "Use of Substituted 2-Aminotetralines for the Preventative Treatment of Parkinson's Disease" (Serial No. 10/585,609).

FIELD OF THE INVENTION

[0000.1] The present invention relates to methods and medicinal preparations for the prevention and/or treatment of Parkinson's plus syndrome.

At page 1, immediately following the paragraph [0000.1] entitled "FIELD OF THE INVENTION," please insert the following new section heading:

BACKGROUND OF THE INVENTION

At page 4, immediately following paragraph [0017], please insert the following section heading and paragraphs:

SUMMARY OF THE INVENTION

[0017.1] There is now provided a method for prevention and/or treatment of a Parkinson's plus syndrome in a patient, the method comprising administering to the patient a compound selected from the group consisting of

rotigotine or physiologically acceptable salts or prodrugs thereof. The Parkinson's plus syndrome prevented or treated herein can be, for example, multiple system atrophies, progressive supranuclear palsy, corticobasal degeneration, diffuse dementia with Lewy bodies or combinations thereof. Common to these diseases subsumed under Parkinson's plus syndrome is a lack of or rapidly diminishing response to L-dopa or other dopamine agonists.

[0017.2] A therapeutic combination is further provided. The combination comprises rotigotine or a physiologically acceptable salt or prodrug thereof and at least one further active substance that prevents or reduces the rate of progression of dopaminergic cell loss in a patient.

[0017.3] In particular embodiments, the compound of the invention may be in a pharmaceutical form wherein the preparation can be administered orally, parenterally, transdermally or transmucosally. When a combination preparation is used, the pharmaceutical form can provide different release profiles for rotigotine and any further active substances.

[0017.4] A kit for treatment and/or prevention of Parkinson's plus syndrome is also provided. The kit includes a first medicinal preparation comprising rotigotine or a physiologically acceptable salt or prodrug thereof and a second medicinal preparation comprising at least one further active substance. The rotigotine and active substances may be administered to a subject simultaneously or in a temporally graduated manner.

At page 4, immediately following paragraph **[0017.4]**, please insert the following new section heading:

DETAILED DESCRIPTION OF THE INVENTION

At page 10, immediately following paragraph **[0069]**, please insert the following new section heading:

EXAMPLES

DELETION(S):

Please delete paragraph **[0007]**.

REPLACEMENT(S):

Please replace paragraphs **[0001]**, **[0003]** – **[0004]**, **[0006]**, **[0008]**, **[0010]**, **[0013]**, **[0016]**, **[0018]**, **[0020]**, **[0022]** – **[0023]**, **[0026]**, **[0030]** – **[0048]**, **[0051]**, **[0054]** – **[0055]**, **[0057]** – **[0058]**, **[0061]** – **[0063]**, and **[0068]** with the following replacement paragraphs provided in amendment format:

[0001] The term ~~Parkinson's plus syndrome~~ "Parkinson's plus syndrome" covers several idiopathic diseases which are associated with the occurrence of symptoms which are Parkinson-like but ~~which~~ that may be differentiated by diagnostic and clinical/pathophysiological means from Parkinson's disease.

[0003] Multiple system atrophies subsume, in particular, Shy-Drager syndrome, olivopontocerebellar atrophy (OPCA) and striatonigral degeneration (SND) ~~(Mark et al, Neurol Clin. 2001, 19(3): 607)~~. *See* Mark et al, Neurol Clin. 2001, 19(3): 607.

[0004] The assignment of Pick's disease, hemiparkinsonism and parkinsonism in Alzheimer's and ALS patients and the Westphal variant of Huntington's chorea to PPS is not uniform in specialist literature, but for the purposes of the present patent application, these diseases ~~should be~~ are considered to be subsumed under the term PPS in accordance with the classification used by Hobson et al, Can J Neurol Sci. 2003 Mar; 30 Suppl 1: p 2 ~~(Hobson et al, Can J Neurol Sci. 2003 Mar; 30 Suppl 1: p 2)~~.

[0006] ~~Table 1 is~~ For an overview of differential-diagnostic criteria and classification of some symptoms for several Parkinson's plus syndromes and Parkinson's disease (also known as idiopathic Parkinson's syndrome, IPS), Table 1 is provided below.

TABLE 1

	Parkinson's plus syndrome				IPS
	Multiple system atrophy		CBD	PSP	
	SND	OPCA			
Rigor/akinesia	++	+	++/+++	++/+++	++/+++
Cerebellar signs	+	++	-	-	-
Pyramidal signs	-	++	++	+	-
Postural instability	+	+	+	+++	+
Dementia	-	-	+	+	+
Oculomotor					
disorders	+	(+)	+	+++	+
Dysphagia	-	+	++	++	+
Retrocollis	-	-	-	++	-
Sphincter disorders	+	+	-	-	-
Impotence	+	+	++	+	+

SND: striatonigral degeneration
CBD: corticobasal degeneration
IPS: idiopathic Parkinson's syndrome
OPCA: olivopontocerebellar atrophy
PSP: progressive supranuclear palsy

[0008] Table 1 is based on ~~(Modified according to~~ Mark MH, Lumping and splitting the Parkinson plus syndromes: dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticalbasal ganglionic degeneration. Neurol Clin. 2001 Aug; 19(3): 607-27. The table is also modified according to ~~and~~ Gerlach M, Reichmann H, Riederer P, Die Parkinson-Krankheit, Springer Vienna New York, ~~2003)~~ 2003.

[0010] Due to the frequently absent or poor response to L-dopa, drug treatment for PPS is difficult and generally consists in a symptomatic therapy for specific individual symptoms, [[eg]] *e.g.* treatment for hypotension.

[0013] Rotigotine, also known as [(-)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphtol], is known from the prior art as a dopamine agonist and symptomatic therapy for Parkinson's disease.

[0016] However, apoptotic processes play an important role in the pathogenesis of Parkinson's plus syndrome in particular with regard to the destruction of dopaminergic neurons. *See*, for example, Lev et al, Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(2): 245; and Michel et al, Rev Neurol (Paris). 2002; 158 Spec no 1: p 24. ~~(Lev et al, Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(2): 245; Michel et al, Rev Neurol (Paris). 2002; 158 Spec no 1: p 24).~~ In addition, as reported in Hirsch et al (Ann N Y Acad Sci. 2003; 991: 214), various other neurodegenerative processes are thought to have a decisive influence on the development of parkinsonism and Parkinson's plus syndrome ~~(Hirsch et al, Ann N Y Acad Sci. 2003; 991: 214)~~.

[0018] As may be seen in Table 2, and Figures 1 and 2, ~~Experimental~~ experimental investigations have now surprisingly revealed that rotigotine, which up to now has only been used for symptomatic therapy of idiopathic Parkinson's disease, has neuroprotective properties in mammals. Rotigotine surprisingly demonstrates the desired pharmacological profile in both an acute and a subacute MPTP model ~~(Table 2, Figures 1 and 2)~~. The results of the investigation suggest that rotigotine prevents apoptotic processes.

[0020] The results set forth below in Table 2 indicate the number ~~Table 2: Number~~ of acutely degenerating neurons in the MPTP mouse model shown with FluoroJade staining with and without treatment with a single administration of rotigotine:

TABLE 2

Group	Number of degenerating neurons	Standard deviation
1: Vehicle-treated control	2.0	2.4
2: MPTP intoxication	73.5	34.0
3: MPTP intoxication + rotigotine 0.3 mg/kg	66.7	30.5
4: MPTP intoxication + rotigotine 1.0 mg/kg	76.8	41.6
5: MPTP intoxication +	34.9	31.9

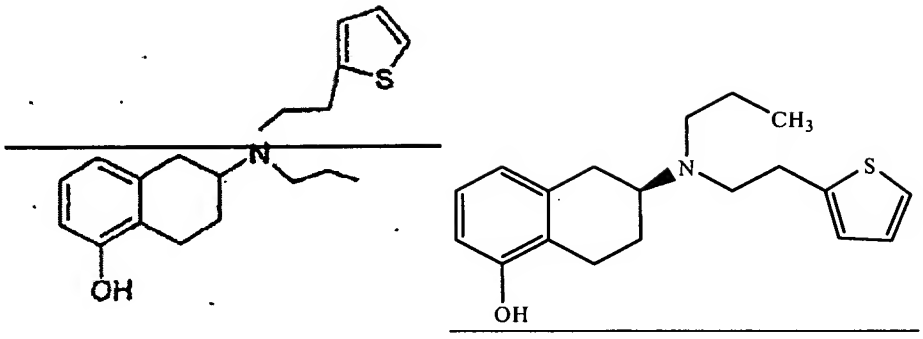
rotigotine 3.0 mg/kg		
6: MPTP-vehicle + rotigotine 3.0 mg/kg	3.8	4.3

[0022] In the MPTP model used, which reflects the progressive course of dopaminergic cell destruction in primates, monkeys (macaques) were injected with subthreshold toxic doses of MPTP over several days. The parkinsonian symptoms developed in the model over a period of approximately 2 weeks. As soon as a specific degree of damage was reached, daily injections of rotigotine were ~~given~~ provided in a formulation giving rise to a continuous plasma level over ~~24 h~~ a 24 hour period. The injections of MPTP were stopped as soon as the motor activity in the controls had reduced by a specific degree (approximately 5 days later). The animals' ~~behaviour~~ behavior was evaluated every day. Six weeks after the commencement of the MPTP application, the injections of rotigotine were stopped and the animals were observed for a further two weeks with no treatment. It was noted that the motor activity of the animals significantly improved under treatment and also in the following wash-out phase.

[0023] At the end of rotigotine application or at the end of the wash-out phase, in each case one group of animals was sacrificed and the condition of the basal ganglia investigated histologically and biochemically. The density of the nerve endings in the striatum of the treated animals was much higher than it was in the untreated animals. The content of preproenkephalin, an indicator of the intact crosslinking in the 'indirect pathway' of the basal ganglia, indicated a tendency toward ~~normalisation~~ normalization after the treatment and after the wash-out phase.

[0026] Compared to the previous use of rotigotine, which was restricted to the purely symptomatic dopaminergic treatment of Parkinson's disease-patients, the treatment of patients with Parkinson's plus syndrome is therefore disclosed as a new field of application and, to be precise, also for patients who do not respond, or respond inadequately, to treatment with L-dopa or dopamine agonists with no neuroprotective action.

[0030] Rotigotine has the following formula:



[0031] Therefore, the relevant prodrugs of rotigotine are in particular derivatives of the phenolic hydroxy group, in particular esters, [[eg]] *e.g.* aryl carbonyl esters, alkyl carbonyl esters or cycloalkyl carbonyl esters, in particular alkyl carbonyl esters and cycloalkyl carbonyl esters each with up to 6 carbon atoms, carbonates, carbamates, acetals, ketals, acyloxyalkyl ethers, phosphates, phosphonates, sulfates, sulfonates, thiocarbonyl esters, oxythiocarbonyl esters, thiocarbamates, ethers and silylethers.

[0032] The term "alkyl carbonyl esters" comprises compounds in which the oxygen atom of rotigotine is in each case bound to [[the]] a -C(O)-alkyl group. An alkyl carbonyl ester is formally formed from the esterification of the phenolic hydroxy group with an alcanoic acid, [[eg]] *e.g.* with acetic acid, propionic acid, butyric acid, isobuyric acid or valeric acid.

[0033] The term "cycloalkyl carbonyl esters" comprises compounds in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(O)-cycloalkyl group.

[0034] The term "aryl carbonyl esters" comprises compounds in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(O)-aryl group.

[0035] The term "carbonates" comprises compounds in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(O)-O-R group.

[0036] The term "carbamates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(O)-NRR1,-C(O)-NH-R1 or -C(O)-NH_2 group.

[0037] The term "acetals" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -CH(OR)R1 group.

[0038] The term "ketals" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(OR)R1R2 group.

[0039] The term "acyloxyalkyl ethers" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -CHR-O-C(O)-R1 or -CH_2-O-C(O)-R1 group.

[0040] The term "phosphates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -P(O_2H)OR group.

[0041] The term "phosphonates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -P(O_2H)R group.

[0042] The term "sulfates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -S$(O)_2$OR group.

[0043] The term "sulfonates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -S$(O)_2$R group.

[0044] The term "thiocarbonyl esters" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(=S)-R group.

[0045] The term "oxythiocarbonyl esters" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(=S)-O-R group.

[0046] The term "thiocarbamates" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -C(=S)-N-RR1,-C(=S)-NH-R1 or-C(=S)-NH_2 group.

[0047] The term "ethers" comprises compounds, in which in each case the oxygen atom of rotigotine is bonded to [[the]] a -R group.

[0048] In the above definitions of prodrugs, each of R, R1, and R2 is independently selected from hydrogen, alkyl, cycloalkyl [[or]] and aryl, and preferably from the group ~~C1-6~~ C_{1-6} alkyl, ~~C3-10~~ C_{3-10} cycloalkyl and phenyl.

[0051] "Aryl" is preferably phenyl. Phenyl can optionally be substituted in one or more positions, [[eg]] *e.g.* with alkoxy, alkyl, halogen or nitro.

[0054] The basic suitability of a rotigotine derivative as a prodrug can be determined by incubating the compound under defined conditions with an enzyme cocktail, a cell homogenate or an enzyme-containing cell fraction and demonstrating that rotigotine can be formed in a sufficient quantity. A suitable enzyme mixture is, for example, contained in the S 9 liver preparation made by the company Firma Gentest, Woburn, Ma, USA ~~(embodiment 5)~~. The use of at least one suitable enzyme mixture is described herein in the 5th embodiment of the Examples. Alternatively, incubation with fresh blood or plasma or even a homogenate of the hypodermis may be performed in order to demonstrate the liver-independent ~~metabolisation~~ metabolization of the prodrug to form the active component. Transdermal application requires an in vitro examination of permeation on excised skin.

[0055] The final evidence of suitability and potential efficacy in the medical models is performed by determining the rotigotine formed from the prodrug in the plasma. ~~: in vivo~~ *In vivo*, a prodrug should release sufficient rotigotine to achieve a therapeutically effective steady-state concentration of rotigotine in the plasma, as is already known from clinical or preclinical investigations. In this regard, effective concentrations are generally rotigotine concentrations of between 0.01 and 50 ng/mL, preferably between 0.05 ng and 20 ng/mL and particularly preferably between 0.1 and 10 ng/mL plasma.

[0057] Rotigotine and its prodrug can be present as free bases or in the form of physiologically acceptable salts, [[eg]] *e.g.* in the form of hydrochloride, in the medicament.

[0058] "Physiologically acceptable salts" include non-toxic addition salts of rotigotine with organic or inorganic acids, [[eg]] *e.g.* rotigotine HCl.

[0061] Preferably, rotigotine is in this regard applied to the patient's skin in plaster form, whereby the active substance is preferably present in a matrix of adhesive polymer, [[eg]] *e.g.* a self-adhesive ~~adhesive~~ polysiloxane. Examples of suitable transdermal formulations may be found in WO 99/49852, WO 02/89777, WO 02/89778, WO 04/58247, WO 04/12730, WO 04/12721 or WO 04/50083. A pharmaceutical form of this kind permits the establishment of an extensively constant plasma level and hence constant dopaminergic stimulation over the entire application interval. *See*, for example, WO 02/89778; or Metman, Clinical Neuropharmacol 24, 2001, 163. ~~(WO 02/89778; Metman, Clinical Neuropharmacol 24, 2001, 163).~~

[0062] If, on the other hand, a medicinal product in the form of a subcutaneous or intramuscular depot form is desired, the rotigotine can, for example, be suspended as a salt crystal, [[eg]] *e.g.* as a crystalline hydrochloride, in a hydrophobic, anhydrous medium and injected, as described in WO 02/15903~~, or~~. Rotigotine can also administered in the form of microcapsules, microparticles or implants based on biodegradable polymers, such as is described, for example, in WO 02/38646.

[0063] Other conceivable forms for the administration of rotigotine and its prodrug are transmucosal formulations, [[eg]] *e.g.* sublingual or nasal sprays, rectal formulations or aerosols for pulmonary administration.

[0068] In a combination preparation, the release of the active substances used in each case can take place to a large extent simultaneously or even sequentially. Sequential administration can, for example, be achieved by a pharmaceutical form, [[eg]] *e.g.* an oral tablet, having two different layers with different release profiles for the different pharmaceutically active components. A combination preparation according to the invention comprising a rotigotine formulation can alternatively also take the form of a "kit of parts"

in which the antiapoptotic active substances to be administered are present in formulations which are separate from each other, which are then administered simultaneously or in a temporally graduated manner.